

09/512829



file copy

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 45/06, 31/44, 31/71, 31/41, 31/43, 9/20, 9/48		A1	(11) International Publication Number: WO 96/24375
			(43) International Publication Date: 15 August 1996 (15.08.96)
(21) International Application Number: PCT/SE96/00125		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 2 February 1996 (02.02.96)		Published <i>With international search report.</i>	
(30) Priority Data: 9500422-2 6 February 1995 (06.02.95) SE			
(60) Parent Application or Grant (63) Related by Continuation US 08/464,775 (CIP) Filed on 7 June 1995 (07.06.95)			
(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).			
(72) Inventors; and (75) Inventors/Applicants (for US only): DEPUY, Helene [FR/SE]; Wrangelsgatan 7B, S-416 62 Göteborg (SE). ROSINSKI, Adam [SE/SE]; Rävekärrsgatan 307, S-431 33 Mölndal (SE).			
(74) Agent: PATENT DEPARTMENT; Astra Aktiebolag, S-151 85 Södertälje (SE).			

(54) Title: **NEW ORAL PHARMACEUTICAL DOSAGE FORM**

(57) Abstract

An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more antibacterial compounds in a fixed formulation. The fixed formulation is intended for oral use and in the form of an enteric coating layered tablet, a capsule or a multiple unit tableted dosage form. The multiple unit dosage form is most preferred. The new fixed formulation is especially useful in the treatment of disorders associated with *Helicobacter* infections.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

NEW ORAL PHARMACEUTICAL DOSAGE FORM

Field of the invention

5 The present invention is related to new oral pharmaceutical preparations especially for use in the treatment of disorders associated with *Helicobacter* infections. The present preparations comprise an acid susceptible proton pump inhibitor in combination with one or more antibacterial compounds in a new fixed unit dosage form, especially a tableted dosage form. Furthermore, the present invention refers to a method for the manufacture of 10 such preparations and the use of such preparations in medicine, especially in the treatment of *Helicobacter pylori* infections.

Background of the invention

15 The relationship between gastrointestinal disorders and infections with *Helicobacter pylori* proposed in 1983 by Warren (Warren JR Lancet 1983;1:1273) is well established today. A number of different therapies have been proposed for treatment of *H. pylori* infections. Most of these therapies comprise different combinations of antibacterial compounds. Some of these therapies also comprise a bismuth compound, see for instance WO 89/03219

20 (Borody). Other combination therapies comprise a proton pump inhibitor and one or more antibacterial compounds, for instance a combined regimen of omeprazole and amoxicillin which has been approved by regulatory authorities in for example Great Britain and Sweden for the treatment of *H. pylori* infections. Different triple therapies, for example omeprazole, clarithromycin and amoxicillin or other antibacterial substances, have recently

25 been reported at the 10th World Congresses of Gastroenterology in October 1994. Some published patent applications in this field are for instance:

WO 93/00327, Astra Aktiebolag, which discloses the combination of a substance with inhibiting effect in the gastric acid secretion which increases the intragastric pH and an

acid degradable antibacterial compound. The proposed combination is especially suitable for the treatment of *H. pylori* infections.

WO 92/03135, Smithkline & French Laboratories, which discloses a combination of a benzimidazole and an anti-*Helicobacter* agent, i.e. for instance pantoprazole in combination with amoxicillin and/or metronidazole.

In these proposed combination therapies each single active substance is administered separately in different dosage forms, each one comprising only one single active substance.

It is well known that patient compliance is a main factor in receiving a good result in medical treatments, especially in the treatment of *H. pylori* infections. Administration of two, three or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more different active substances combined in one fixed unit dosage form, preferably a tablet.

It is well known that proton pump inhibitors are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, it is obvious that one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of omeprazole as well as other proton pump inhibitors described in the prior art, see for example US-A 4,786,505 (AB Hässle).

There are problems to produce a fixed unit dosage form comprising a rather high amount of active substances. Different active substances in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets containing acid susceptible proton pump inhibitors as active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be

destroyed upon administration by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

Summary of the invention

5

The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, enteric coating layered tablets, multilayered tablets or a capsule filled with more than one pharmaceutically active compound. The active compounds present are preferably an acid susceptible proton pump inhibitor and one or more antibacterial 10 substances. These new dosage forms will simplify the regimen and improve the patient compliance.

Description of the Figures

15 Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with an antibacterial granulation (2). The tablet is covered by an overcoating layer (7).

20 Fig. 2 illustrates a cross-section of a tablet with two separate layers, one layer comprises enteric coating layered pellets of an acid susceptible proton pump inhibitor (1) in admixture with excipients (3) and the other layer comprises the antibacterial compound(s) (2). The tablet is covered by an overcoating layer (7).

25 Fig. 3 illustrates a cross-section of an enteric coating layered tablet comprising an acid susceptible proton pump inhibitor in admixture with one or more antibacterial substances (4). The tablet is covered by an enteric coating layer (7).

Fig. 4 illustrates an enteric coating layered tablet consisting of two separate layers, one layer comprises an acid susceptible proton pump inhibitor (5) and the other layer comprises the antibacterial compound(s) (6).

5 Detailed description of the invention

One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units together with one or more antibacterial compounds in the form of a 10 powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability during long-term storage to the active substances. 15 Alternatively, the prepared tablet has separate layers, one layer is in the form of compressed enteric coated layered units comprising the proton pump inhibitor and another layer comprises the antibacterial compound(s).

The new fixed dosage form is preferably in the form of a multiple unit tableted dosage 20 form comprising enteric coating layered units of the one of the active substance which is acid susceptible, i.e. the proton pump inhibitor, and granules of the other active substance(s), i.e. the antibacterial granulation, as shown in Figs. 1 and 2. Alternatively, the different active compounds may be intimately mixed with each other and compressed into a conventional tablet, which is enteric coated as shown in Figs. 3 and 4. As a further 25 alternative, the different active substances are dry mixed and filled into a capsule. In the latter preparation the acid susceptible proton pump inhibitor is in the form of enteric coating layered units (1).

Another object of the invention is to provide a tablet preparation comprising an acid susceptible proton pump inhibitor in admixture with one or more antibacterial substances compressed into a tablet, which tablet is enteric coating layered. Optionally a separating layer is applied before the tablet is enteric coating layered. Alternatively, the prepared tablet core has separate layers, each one comprising different active substances. One of the layers comprises the acid susceptible proton pump inhibitor and another layer(s) comprises(-e) the antibacterial substance or substances, respectively. The prepared tablet is thereafter enteric coating layered.

10 A further object of the invention is to provide a dosage form which is divisible, such as divisible tablets.

Still a further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. The multiple unit tableted dosage form may be dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

Furthermore, the present invention provides a capsule preparation comprising the acid susceptible proton pump inhibitor in the form of enteric coating layered pellets mixed with one or more antibacterial compounds in the form of granules or pellets.

25 The antibacterial components may be formulated in the form of instant release, sustained release or extended release formulations. Alternatively, the components may be formulated in an effervescent formulation.

The new fixed unit dosage forms comprise as active substances an acid susceptible proton pump inhibitor and one or more antibacterial compounds. The different active components used in the dosage forms are defined below.

Active substances

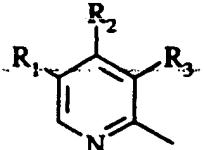
The proton pump inhibitors are for example compounds of the general formula I



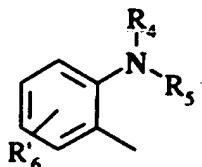
wherein

Het₁ is

10

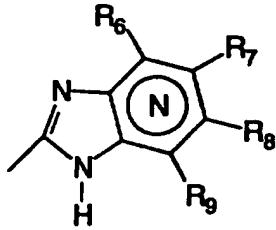


or

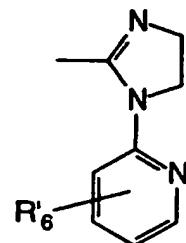
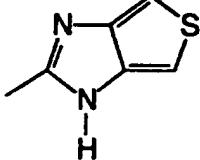


Het₂ is

or

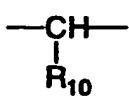


or

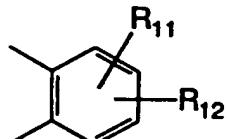


X =

15



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

20

R_1 , R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

5 R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

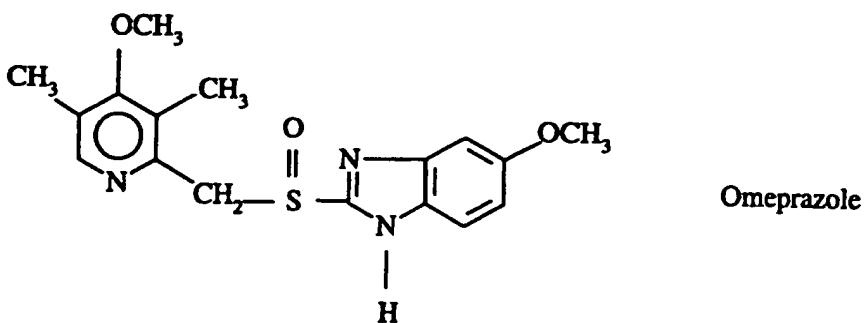
10 R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6 - R_9 , form ring structures which may be further substituted;

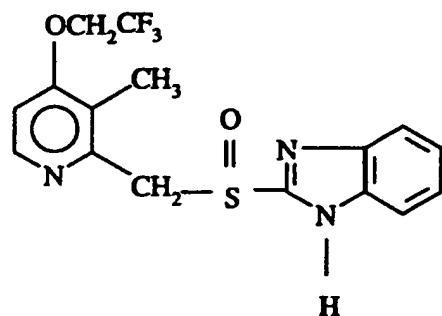
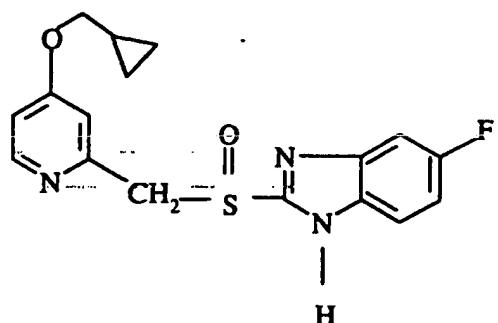
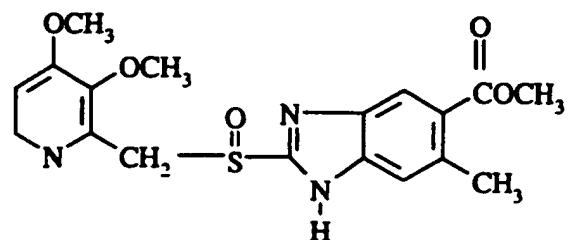
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

15 R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl and alkyl groups, alkoxy groups and moieties thereof may be branched and straight C₁-C₉-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

Examples of proton pump inhibitors according to formula I are

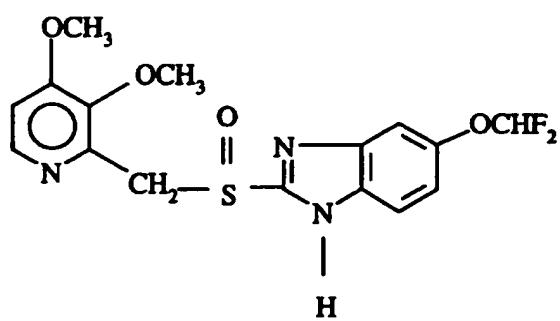
20





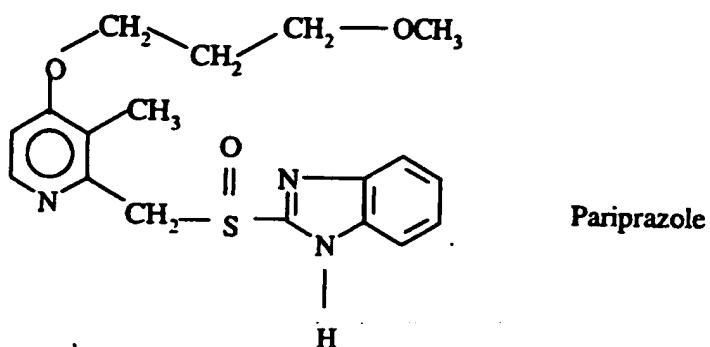
Lansoprazole

5

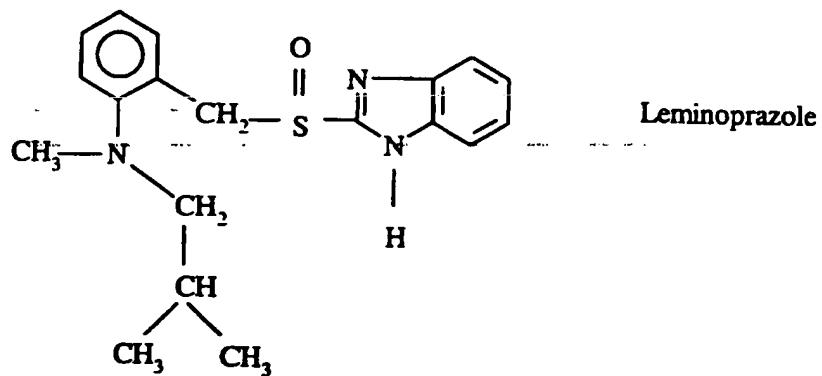


Pantoprazole

9

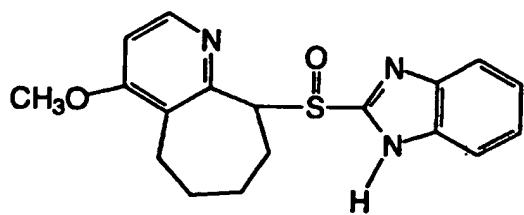
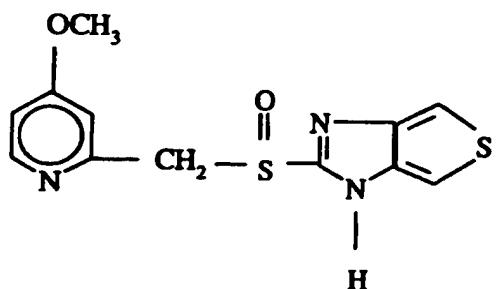


Pariprazole

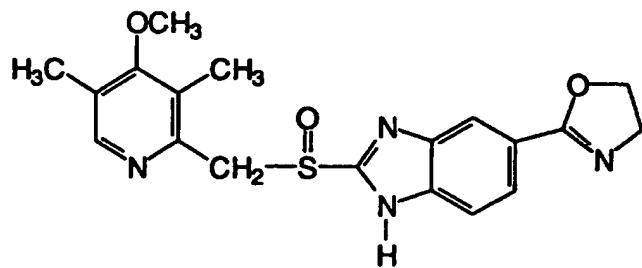
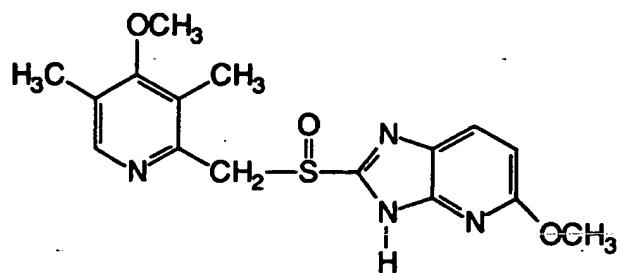
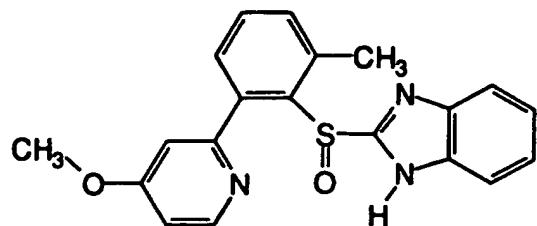


Leminoprazole

5



10



5

The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above

10 may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, 15 WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO94/27988.

A wide variety of antibacterial compounds may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such antibacterial compounds include for example nitroimidazole antibiotics, tetracyclines, penicillins, cephalosporins, carbopenems, aminoglycosides, macrolide antibiotics, 5 lincosamide antibiotics, 4-quinolones, rifamycins and nitrofurantoin. In the following examples of such antibacterial compounds are listed: ampicillin, amoxicillin, benzylpenicillin, phenoxyethylpenicillin, bacampicillin, pivampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin, methicillin, oxacillin, piperacillin, ticarcillin, flucloxacillin, cefuroxime, cefetamet, cefetrame, cefixime, cefoxitin, ceftazidime, 10 ceftrizoxime, latamoxef, cefoperazone, ceftriaxone, cefsulodin, cefotaxime, cephalexin, cefaclor, cefadroxil, cefalothin, cefazolin, cefpodoxime, ceftibuten, aztreonam, tigemonam, erythromycin, dirithromycin, roxithromycin, azithromycin, clarithromycin, clindamycin, palidomycin, lincomycin, vancomycin, spectinomycin, tobramycin, paromomycin, metronidazole, tinidazole, ornidazole, amifloxacin, cinoxacin, 15 ciprofloxacin, difloxacin, enoxacin, fleroxacin, norfloxacin, ofloxacin, temafloxacin, doxycycline, minocycline, tetracycline, chlortetracycline, oxytetracycline, methacycline, rolitetracyclin, nitrofurantoin, nalidixic acid, gentamicin, rifampicin, amikacin, netilmicin, imipenem, cilastatin, chloramphenicol, furazolidone, nifuroxazide, sulfadiazin, sulfametoxazol, bismuth subsalicylate, colloidal bismuth subcitrate, gramicidin, 20 mecinam, cloxiquine, chlorhexidine, dichlorobenzylalcohol, methyl-2-pentylphenol. The active antibacterial agents could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above listed drugs may be used, for example to minimize the risk for developing resistance. Preferable antibacterial compounds for the new fixed dosage form are clarithromycin, erythromycin, roxithromycin, azithromycin, 25 amoxicillin, metronidazole, tinidazole and tetracycline. Clarithromycin and metronidazole alone or in combination are especially suitable.

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor in the form of a racemat, an alkaline salt or one of its single enantiomers and one or more 30 antibacterial compounds, is characterized in the following way. Individually enteric coating

layered units (small beads, granules or pellets) containing the acid susceptible proton pump inhibitor and optionally containing alkaline reacting substances, are mixed with the antibacterial compound(s) and conventional tablet excipients. Preferably, the antibacterial compound(s) and tablet excipients are in the form of a granulation. The dry mixture of

5 enteric coating layered units, antibacterial granulation and optionally excipients are compressed into the multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the proton pump inhibitor.

10 The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid

15 resistance does not decrease more than 10% during the compression of the pellets into tablets.

20 The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid

25 Chromatography (HPLC).

Further specific components used in the fixed unit dosage forms of the present invention are defined below.

Core material - for enteric coating layered pellets comprising a proton pump inhibitor

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the acid susceptible proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

Th: seeds which are to be layered with the acid susceptible proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc.

The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example are celluloses such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl-cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), sugar or starch or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing

conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

5

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives.

10

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

15

20

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

25

Enteric coating layer(s)

30

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets, the pellets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline compounds such as

pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s).

The separating layer(s) can be applied to the core material by coating or layering 5 procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, 10 polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, water soluble salts of enteric coating polymers and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be 15 included into the separating layer(s).

When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and 20 may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3.6\text{MgO}.\text{CO}_2.12\text{H}_2\text{O}$, 25 $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3.4\text{H}_2\text{O})$, $\text{MgO}.\text{Al}_2\text{O}_3.2\text{SiO}_2.\text{nH}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other 30 compounds may be added to increase the thickness of the layer(s) and thereby strengthen

the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

5

Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material and an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a water soluble salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in 10 the position to form a salt.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic 15 solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

20

The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other 25 plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness 30 of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so

that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

10 To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating is normally only limited by processing conditions.

15 Alternatively the enteric coating layer described above may be used for enteric coating layering of conventional tablets comprising a composition of an acid susceptible proton pump inhibitor and one or more antibacterial compounds, optionally covered by one of the separating layers described above. As a further alternative, the proton pump inhibitor may 20 be replaced in such a tablet by another gastric acid suppressing agents, such as a H_2 -receptor antagonist, for instance ranitidine, cimetidine or famotidine.

Over-coating layer

25 Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among 30 pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol,

polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, 5 titanium dioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further it may protect the enteric coating layer towards cracking during the compaction process and enhance the tabletting process. The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

10

The above described over-coating layer may also be used as a tablet coating layer to obtain tablets of good appearance.

Antibacterial granulation

15

The active substance in the form of one or more antibacterial compounds is dry mixed with inactive excipients and the mixture is wet massed with a granulation liquid. The wet mass is dried preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, and preferably smaller 20 than 1 mm. Suitable inactive excipients for the antibacterial granulation are for instance, sodium starch glycolate, corn starch, crosslinked polyvinyl pyrrolidone, low substituted hydroxypropyl cellulose, microcrystalline cellulose and colloidal silicon dioxide anhydrous (Aerosil®). The dry mixture comprising antibacterial compound(s) is mixed with a suitable granulation liquid comprising for instance, polyvinyl pyrrolidone, hydroxypropyl cellulose, 25 and optionally wetting agents, such as sodium lauryl sulphate, dissolved in purified water. Suitable lubricants for the tabletting process are for instance, sodium stearyl fumarate, magnesium stearate and talc.

Multiple unit tablets

30

The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the granules comprising antibacterial compounds and tablet excipients. The dry mixture is compressed into a multiple unit tableted dosage form. The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further

5 enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives such as anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

10 The enteric coated pellets with or without an over-coat and the antibacterial granulation are mixed with tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives and compressed into tablets.

15 The amount of enteric coating layered pellets constitutes less than 75 % by weight of the total tablet weight and preferably less than 60 %. By choosing small enteric coating layered pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy. Larger amount of the granulation comprising the antibacterial compound(s) may reduce the amount of enteric coating layered pellets in the multiple unit tableted dosage form.

20

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of an acid susceptible proton pump inhibitor, optionally mixed with alkaline reacting compound(s), compressed into tablet together with a granulation containing antibacterial compound(s) and optionally tablet excipients. The addition of an alkaline reacting material to the proton pump inhibitor is not necessary, in any sense but such a substance may further enhance the stability of the proton pump inhibitor or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating layer. The enteric coating layer(s) is making the pellets of the dosage form insoluble in acidic media, but disintegrating/dissolving in

25 near neutral to alkaline media such as, for instance the liquids present in the proximal part

of the small intestine, where dissolution of the proton pump inhibitor is desired. The antibacterial substance(s) may be released in the stomach. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the tablet and they may also contain one or more separating layer(s) optionally containing 5 alkaline substance(s).

Process

10 The process for the manufacture of the dosage form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and then with the enteric coating layer(s) or a separating layer is spontaneously developed 15 in situ between an alkaline core material and the enteric coating layer material. The coating is carried out as described above and in the accompanying examples. The preparation of the granulation comprising the antibacterial compound(s) is also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

20 The enteric coating layered pellets, with or without an over-coat, are mixed with the prepared granules, tablet excipients and other pharmaceutical acceptable additives and compressed into tablets. The tablet may be in the form of a two layer tablet, wherein one layer comprises the enteric coating layered pellets optionally mixed with inactive 25 excipients and the other layer comprises the prepared granules of the antibacterial substance(s). Alternatively, the different active substances in the form of powders may be intimately dry mixed with tablet excipients, wet massed and compressed into conventional tablets before applying an optional separating layer and an enteric coating layer. The tablet may be in the form of a two layer enteric coating layered tablet, wherein one layer comprises one of the active substances and the other layer comprises the other active substance(s). As a further alternative, the proton pump inhibitor in the form of enteric

coating layered pellets may be filled in a capsule together with the antibacterial substance(s) in the form of a granulation optionally mixed with pharmaceutical excipients.

Use of the preparation

5

The dosage forms according to the invention are especially advantageous in the treatment of *H. pylori* infections. They are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of 10 administration and disease. In general each dosage form will comprise 0,1-200 mg of the proton pump inhibitor and 0,1 mg - 1,2 g of the antibacterial compound(s). Preferably, each dosage form will comprise 10-80 mg of the proton pump inhibitor and 100-900 mg of the antibacterial compound(s), and more preferably 20-40 mg of proton pump inhibitor and 250-650 mg of the antibacterial compound(s), respectively.

15

The multiple unit tablet preparation is also suitable for dispersion in an aqueous liquid with neutral or slightly acidic pH-value before being orally administered or fed through a nasogastric tube.

20 The invention is illustrated more in detail in the following examples.

Examples

Example 1:

25

Multiple unit dosage form comprising omeprazole and metronidazole (batch size 10.000 tablets).

Core material

30 Magnesium omeprazole 12.00 kg

	Sugar sphere seeds	12.00 kg
	Hydroxypropyl methylcellulose	1.8 kg
	Water purified	35.4 kg
5	<u>Separating layer</u>	
	Core material (acc. to above)	23.50 kg
	Hydroxypropyl cellulose	2.35 kg
	Talc	4.03 kg
	Magnesium stearate	0.34 kg
10	Water purified	48.00 kg
	<u>Enteric coating layer</u>	
	Pellets covered with separating layer (acc. to above)	29.00 kg
	Methacrylic acid copolymer (30% suspension)	38.70 kg
15	Triethyl citrate	3.48 kg
	Mono- and diglycerides (NF)	0.58 kg
	Polysorbate 80	0.06 kg
	Water purified	22.68 kg
20	<u>Over-coating layer</u>	
	Enteric coating layered pellets (acc. to above)	44.7 kg
	Hydroxypropyl methylcellulose	0.58 kg
	Water purified	11.6 kg
25	<u>Tablets</u>	
	Prepared pellets comprising omeprazole as prepared above	933 g
	Metronidazole	4000 g
	Sodium starch glycolate	500 g
	Aerosil®	25 g
30	Sodium lauryl sulphate	20 g

Polyvidone K90	253.1 g
Microcrystalline cellulose	1181 g
Water purified	2278 g
Sodium stearyl fumarate	66.5 g

5

Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
Titanium dioxide	62.5 g
Water purified	2125 g
Hydrogen pyroxide	0.75 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

15 The size of sugar sphere seeds are in the range of 0.25 to 0.35 mm.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl 20 citrate and polysorbate is sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets are coated with hydroxypropyl methylcellulose solution. The over-coating layered pellets are classified by sieving.

25 Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Metronidazole, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steamoven at 50°C. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

The enteric coating layered pellets with an over-coating layer, prepared granules, microcrystalline cellulose and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x17 mm oval punches. The amount of omeprazole in each tablet is approx. 20 mg and the amount of metronidazole is approx. 400 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 20 kN. 5 Tablet hardness measured is 150-164N.

The obtained tablets are covered with a conventional tablet coating layer.

10 Example 2:

Multiple unit dosage form comprising omeprazole and clarithromycin (batch size 10.000 tablets).

15 Tablets

Enteric coating layered pellets with an over-coating layer	978 g
(manufacturing and composition as in example 1)	
Clarithromycin	2500 g
Microcrystalline cellulose	3000 g
20 Sodium starch glycolate	350 g
Aerosil®	40 g
Sodium lauryl sulphate	12.5 g
Polyvidone K90	384.8 g
Water purified	3463 g
25 Magnesium stearate	105 g

Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
30 Titanium dioxide	62.5 g

Water purified	2125 g
Hydrogen pyroxide	0.75 g

5 Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Clarithromycin, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

10 The enteric coating layered pellets with an over-coating layer, prepared granules and magnesium stearate are mixed and compressed into tablets as in example 1. The amount of omeprazole in each tablet is approx. 20 mg and the amount of clarithromycin is approx. 250 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 14kN. Tablet hardness measured is 178-189N.

15

The obtained tablets are covered with a conventional tablet coating layer.

Example 3:

20 Multiple unit dosage form comprising omeprazole and clarithromycin (batch size 10.000 tablets).

Tablets

Enteric coating layered pellets with an over-coating layer	978 g
25 (manufacturing and composition as in example 1)	
Clarithromycin	5000 g
Microcrystalline cellulose	2500 g
Sodium starch glycolate	350 g
Aerosil®	40 g
30 Sodium lauryl sulphate	25 g

	Polyvidone K90	361.9 g
	Water purified	3257 g
	Magnesium stearate	91.7 g
5 <u>Tablet coating solution (for 10 kg tablets)</u>		
	Hydroxypropyl methylcellulose	250 g
	Polyethylene glycol 6000	62.5 g
	Titanium dioxide	62.5 g
	Water purified	2125 g
10	Hydrogen pyroxide	0.75 g

The antibacterial granulation is manufactured as in example 2. Enteric coating layered pellets with an over-coating layer, prepared granules and magnesium stearate are mixed and compressed into tablets using a rotary tabletting machine equipped with 10x21 mm oval punches. The amount of omeprazole in each tablet is approx. 20 mg and the amount of clarithromycin is approx. 500 mg. Tabletting speed is set to 50 rpm and the upper punch force is set to 20kN. Tablet hardness measured is 105-128N.

The obtained tablets are covered with a conventional tablet coating layer.

20

Example 4:

Multiple unit dosage form comprising, metronidazole and clarithromycin (batch size 2.500 tablets).

25

Core material

	Magnesium omeprazole	15.00 kg
	Sugar sphere seeds	15.00 kg
	Hydroxypropyl methylcellulose	2.25 kg
30	Water purified	40.25 kg

Separating layer

	Core material (acc. to above)	15.00 kg
	Hydroxypropyl cellulose	1.5 kg
5	Talc	2.57 kg
	Magnesium stearate	0.21 kg
	Water purified	30.00 kg

Enteric coating layer

10	Pellets covered with separating layer (acc. to above)	18.00 kg
	Methacrylic acid copolymer (30% suspension)	30.00 kg
	Triethyl citrate	2.7 kg
	Mono- and diglycerides (NF)	0.49 kg
	Polysorbate 80	0.05 kg
15	Water purified	19.00 kg

Tablets

	Enteric coating layered pellets (acc. to above)	246 g
	Clarithromycin	625 g
20	Metronidazole	1000 g
	Microcrystalline cellulose	375 g
	Sodium starch glycolate	125 g
	Aerosil®	10 g
	Sodium lauryl sulphate	8 g
25	Polyvidone K90	117.8 g
	Water purified	1060 g
	Sodium stearyl fumarate	48.2 g

30 Suspension layering is performed in a fluid bed apparatus. Magnesium meprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl 5 citrate and polysorbate is sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets are classified by sieving.

Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the 10 granulation liquid. Clarithromycin, metronidazole, microcrystalline cellulose, sodium starch glycolate and Aerosil are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

Enteric coating layered pellets, prepared granules and sodium stearyl fumarate are mixed 15 and compressed into tablets as in example 3. The amount of omeprazole in each tablet is approx. 20 mg, the amount of metronidazole is 400 mg and the amount of clarithromycin is 250 mg. Tableting speed is set to 50 rpm and the upper punch force is set to 24 kN. Tablet hardness measured is 130-142N.

20 **Example 5:**

Multiple unit dosage form comprising lansoprazole and clarithromycin (batch size 1.000 tablets).

25 **Core material**

Lansoprazole	400 g
Sugar sphere seeds	400 g
Hydroxypropyl methylcellulose	80 g
Water purified	1200 g

Separating layer

Core material (acc. to above)	400 g
Hydroxypropyl cellulose	40 g
Talc	69 g
5 Magnesium stearate	6 g
Water purified	800 g

Enteric coating layer

Pellets covered with a separating layer (acc. to above)	400 g
10 Methacrylic acid copolymer (30% suspension)	667 g
Triethyl citrate	60 g
Mono- and diglycerides (NF)	10 g
Polysorbate 80	1 g
Water purified	391 g

15

Tablets

Enteric coating layered pellets (acc. to above)	89.8 g
Clarithromycin	250 g
Microcrystalline cellulose	300 g
20 Sodium starch glycolate	35 g
Aerosil®	4 g
Sodium lauryl sulphate	1.25 g
Polyvidone K90	45.2 g
Water purified	406.8 g
25 Magnesium stearate	10.1 g

Suspension layering is performed in a fluid bed apparatus. Lansoprazole is sprayed onto the sugar sphere seeds from a suspension containing the dissolved binder in a water solution.

Pellets covered with separating layer and enteric coating layer are produced as in example

30 1. The antibacterial granulation is manufactured as in example 2.

Enteric coating layered pellets, prepared granules and magnesium stearate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x17 mm oval punches. The amount of lansoprazole in each tablet is approx. 20 mg and the amount of 5 clarithromycin is approx. 250 mg. The upper punch force is set to 5.8 kN, and the tablet hardness is measured 63N.

Example 6.

10 Multiple unit dosage form comprising (s)-omeprazole magnesium salt, metronidazole and clarithromycin (batch size 200 tablets).

Core material

15	(s)-Omeprazole magnesium salt	120 g
15	Sugar sphere seeds	150 g
	Hydroxypropyl methylcellulose	18 g
	Polysorbate 80	2.4 g
	Water purified	562 g

20 **Separating layer**

	Core material (acc. to above)	200 g
	Hydroxypropyl cellulose	30 g
	Talc	51.4 g
	Magnesium stearate	4.3 g
25	Water purified	600 g

Enteric coating layer

30	Pellets covered with separating layer (acc. to above)	250 g
	Methacrylic acid copolymer (30% suspension)	333.7 g
	Triethyl citrate	30 g

Mono- and diglycerides (NF)	5 g
Polysorbate 80	0.5 g
Water purified	196 g

5 Metronidazole and clarithromycin granulation

Clarithromycin	3500 g
Metronidazole	5600 g
Microcrystalline cellulose	1400 g
Sodium starch glycolate	700 g
10 Aerosil®	56 g
Polyvidon K90	511 g
Water purified	4600 g

Tablets

15 Pellets comprising (s)-omeprazole Mg-salt (acc. to above)	25.5 g
Granulation comprising clarithromycin and metronidazole (acc. to above)	168.1 g
Microcrystalline cellulose	40 g
Sodium stearyl fumarate	4.7 g

20

Tablet coating solution (for 10kg tablets)

Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
Titanium dioxide	62.5 g
25 Water purified	2125 g
Hydrogen pyroxide	0.75 g

Suspension layering is performed in a fluid bed apparatus. (s)-Omeprazole magnesium salt is sprayed onto sugar sphere seedes from a water suspension containing the dissolved

binder and polysorbate 80. The size of sugar sphere seedes are in the range of 0.25 to 0.35 mm.

5 The prepared core material is covered with a separating layer in a fluid bed apparatus with hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono-and diglycerides, triethyl citrate and polysorbate is sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets are classified by sieving.

10 Polyvidone K90 is dissolved in purified water to form the granulation liquid. Clarithromycin, metronidazole, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1mm in an oscillating mill equipment.

15 The enteric coating layered pellets, prepared granules, microcrystalline cellulose and magnesium stearate are mixed and compressed into tablets on a tableting machine equipped with 10x21 mm oval punches. The amount of (s)-omeprazole is approx. 20 mg, the amount of metronidazole is approx. 400 mg and the amount of clarithromycin is approx. 250 mg. Tablet hardness tested with a Schleuniger apparatus was 140-150N.

20 The obtained tablets are covered with a conventional tablet coating layer.

25 The results from tests on acid resistance of the compressed tablets are disclosed in Table 1, below.

Table 1

Example No	Acid resistance, tablets (%), n=3
------------	--------------------------------------

2	99
3	91
4	92
5	90
6	93

Example 7:

10 An enteric coating layered tablet comprising magnesium omeprazole, clarithromycin and metronidazol (batch size 1.000 tablets).

Tablets

Magnesium omeprazole	20 g
Clarithromycin	250 g
15 Metronidazole	400 g
Microcrystalline cellulose	150 g
Sodium starch glycolate	50 g
Aerosil®	4 g
Sodium lauryl sulphate	3.2 g
20 Polyvidone K90	50 g
Water purified	450 g
Sodium stearyl fumarate	18 g

Solution for separating layer (for 10 kg tablets)

25 Hydroxypropyl methylcellulose	300 g
Hydrogen peroxide (30%)	0.003 g
Water purified	2700 g

Solution for enteric coating layer (for 10 kg tablets)

30 Methacrylic acid copolymer dispersion (30%)	2450 g
--	--------

Polyethylene glycol 400	80 g
Titanium dioxide	100 g
Water purified	1960 g

5 Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Magnesium omeprazole, clarithromycin, metronidazole, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry-mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an
 10 oscillating mill equipment.

The prepared granules and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tabletting machine equipped with 8.5x19 mm oval punches. The amount of omeprazole in each tablet is 20 mg, the amount of clarithromycin is 250 mg and the
 15 amount of metronidazole is 400 mg.

The obtained tablets are covered with a separating layer and an enteric tablet coating layer.

Example 8:

20 An enteric coating layered tablet comprising lansoprazole and clarithromycin (batch size 1.000 tablets).

<u>Tablets</u>	
25 Lansoprazole	20 g
Clarithromycin	250 g
Microcrystalline cellulose	150 g
Sodium starch glycolate	50 g
Aerosil	4 g
30 Sodium lauryl sulphate	3.2 g

Polyvidone K90	50 g
Water purified	450 g
Sodium stearyl fumarate	18 g

5 Solution for separating layer (for 10kg tablets)

Hydroxypropyl methylcellulose	300 g
Hydrogen peroxide (30%)	0.003 g
Water purified	2700 g

10 Solution for enteric coating layer (for 10 kg tablets)

Methacrylic acid copolymer dispersion (30%)	2450 g
Polyethylene glycol 400	80 g
Titanium dioxide	100 g
Water purified	1960 g

15

Sodium lauryl sulphate and polyvidone K90 are dissolved in purified water to form the granulation liquid. Lansoprazole, clarithromycin, microcrystalline cellulose, sodium starch glycolate and Aerosil® are dry- mixed. The granulating liquid is added to the powder mixture and the mass is wet-mixed. The wet mass is dried in a steam-oven. The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

20

The prepared granules and sodium stearyl fumarate are mixed and compressed into tablets using a rotary tableting machine equipped with 8.5x19 mm oval punches. The amount of lansoprazole in each tablet is 20 mg, the amount of clarithromycin is 250 mg.

25

The obtained tablets are covered with a separating layer and an enteric tablet coating layer.

Example 9:

30 A capsule formulation comprising meprazole and metronidazol.

Core material

	Magnesium omeprazole	10.00 kg
	Sugar sphere seeds	10.00 kg
5	Hydroxypropyl methylcellulose	1.5 kg
	Water purified	29.65 kg

Separating layer

	Core material (acc. to above)	20.00 kg
10	Hydroxypropyl cellulose	2.00 kg
	Talc	3.43 kg
	Magnesium stearate	0.29 kg
	Water purified	40.00 kg

Enteric coating layer

	Pellets covered with a separating layer (acc. to above)	24.00 kg
	Methacrylic acid copolymer (30% suspension)	40.00 kg
	Triethyl citrate	3.6 kg
	Mono- and diglycerides (NF)	0.6 kg
20	Polysorbate 80	0.06 kg
	Water purified	24.45 kg

Metronidazole granulation

	Metronidazole	5000 g
25	Polyvidone K90	62.6 g
	Water purified	562.9 g

Polyvidon K90 is dissolved in purified water to form the granulation liquid. The liquid is added to metronidazole and the mass is wet-mixed. The wet mass is dried in a steam ven.

30 The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

Capsules

Metronidazole granulation (acc. to above)	1250.8 g
Enteric coating layered pellets (acc. to above)	104 mg/capsule
5 (manufacturing as in Example 4)	
Magnesium stearate	24.8 g

10 The metronidazole granulation is mixed with magnesium stearate. Prepared granules and enteric coating layered pellets are filled into capsules, size 0, using a capsule filling machine equipped with powder dosing unit and pellet filler. The amount of omeprazole in each capsule is 20 mg and the amount of metronidazole is 400 mg. Capsule filling speed is set to 61 rpm.

Example 10:

15

A capsule formulation comprising omeprazole and clarithromycin.

Core material

Magnesium omeprazole	15.00 kg
20 Sugar sphere seeds	15.00 kg
Hydroxypropyl methylcellulose	2.25 kg
Water purified	44.00 kg

Separating layer

Core material (acc. to above)	30.00 kg
Hydroxypropyl cellulose	3.00 kg
Talc	5.14 kg
Magnesium stearate	0.43 kg
Water purified	60.00 kg

Enteric coating layer

Pellets covered with a separating layer (acc. to above)	750 g
Methacrylic acid copolymer	322.5 g
Triethyl citrate	96.8 g
5 Mono- and diglycerides (NF)	16.1 g
Polysorbate 80	1.61 g
Water purified	631.4 g

Over-coating layer

10 Hydroxypropyl methylcellulose	22.5 g
Water purified	427.5 g

Clarithromycin granulation

Clarithromycin	5000 g
15 Ethanol (99.5%)	2064 g
Sodium lauryl sulphate	50 g

Sodium lauryl sulphate is dissolved in ethanol to form the granulation liquid. The liquid is added to clarithromycin and the mass is wet-mixed. The wet mass is dried in a steam oven.

20 The prepared granulation is milled through sieve 1 mm in an oscillating mill equipment.

Capsules

Clarithromycin granulation (acc. to above)	1500 g
Hydroxypropyl cellulose (L-HPC)	75 g
25 Magnesium stearate	31.5 g
Pellets covered with an overcoating layer (acc. to above and manufacturing as in example 1)	96.7 mg/capsule

The clarithromycin granulation is mixed with L-HPC and magnesium stearate and capsules of size 00 is filled as in example 8. The amount of omeprazole in each capsule is 20 mg and the amount of clarithromycin is 500 mg.

5 Example 11:

A capsule formulation comprising omeprazole, clarithromycin and metronidazole.

Capsules

10	Clarithromycin granulation (manufacturing and composition as in example 9)	1805 g
	Hydroxypropyl cellulose (L-HPC)	90.3 g
	Metronidazole	2670 g
	Magnesium stearate	91.3 g
15	Pellets covered with an overcoating layer (manufacturing and composition as example 1)	96.7 mg/capsule

The clarithromycin granulation is mixed with metronidazole, L-HPC and magnesium stearate. Capsules of size 00 is filled as in example 8. The amount of omeprazole in each capsule is 20 mg, the amount of metronidazole is 400 mg and the amount of clarithromycin is 250 mg.

Example 12:

A dosage form comprising lansoprazole and clarithromycin, filled into capsules in the form of granules.

Core material

Lansoprazole	400 g
Sugar sphere seeds	400 g
30 Hydroxypropyl methylcellulose	80 g

	Water purified	1200 g
<u>Separating layer</u>		
	Core material (acc. to above)	400 g
5	Hydroxypropyl cellulose	40 g
	Talc	69 g
	Magnesium stearate	6 g
	Water purified	800 g
10	<u>Enteric coating layer</u>	
	Pellets covered with separating layer (acc. to above)	400g
	Methacrylic acid copolymer (30% suspension)	667 g
	Triethyl citrate	60 g
	Mono- and diglycerides (NF)	10 g
15	Polysorbate 80	1 g
	Water purified	391 g
<u>Clarithromycin granulation</u>		
	Clarithromycin	5000 g
20	Ethanol (99.5%)	2064 g
	Sodium lauryl sulphate	50 g
Sodium lauryl sulphate is dissolved in ethanol to form the granulation liquid. The liquid is added to clarithromycin and the mass is wet-mixed. The wet mass is dried in a steam oven.		
25	The prepared granulation is milled through sieve 1mm in an oscillating mill equipment.	
<u>Capsules</u>		
	Clarithromycin granulation (acc. to above)	1500 g
	Hydroxypropyl cellulose (L-HPC)	75 g
30	Magnesium stearate	31.5 g

Enteric coating layered pellets (acc. to above and
manufacturing as in example 5) 94 mg/capsule

5 The clarithromycin granulation is mixed with L-HPC and magnesium stearate and capsules
of size 00 is filled as in example 8. The amount of lansoprazole in each capsule is 20 mg
and the amount of clarithromycin is 500 mg.

10 The best mode to carry out the invention are dosage forms of the compositions described in
Examples 3, 4 and 6.

15 The enteric coating layered pellets and other intermediate products used in the
compositions described above, may also be prepared as described in the following
examples.

15 Example 13

Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material

20	Magnesium omeprazole	600 g
	Mannitol	1000 g
	Microcrystalline cellulose	300 g
	Hydroxypropyl cellulose	100 g
	Sodium lauryl sulphate	6 g
25	Water purified	802 g

Separating layer

30	Core material (acc. to above)	400 g
	Hydroxypropyl methylcellulose	48 g
	Water purified	960 g

Enteric coating layer

Pellets covered with separating layer (acc. to above)	200 g
Methacrylic acid copolymer	100 g
5 Triethyl citrate	30 g
Mono- and diglycerides (NF)	5 g
Polysorbate 80	0.5 g
Water purified	309 g

10 Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid. Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

15 The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

20 The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

Example 14

Preparation of enteric coating layered pellets by powder.

5 Core material

Magnesium omeprazole	1 500 g
Sugar sphere seeds	1 500 g
Hydroxypropyl methylcellulose	420 g
Aerosil®	8 g
10 Water purified	4 230 g

Separating layer

Core material (acc. to above)	500 g
Hydroxypropyl cellulose	40 g
15 Talc	67 g
Magnesium stearate	6 g
Water purified	800 g

Enteric coating layer

20 Pellets covered with separating layer (acc. to above)	500 g
Methacrylic acid copolymer	200 g
Triethyl citrate	60 g
Water purified	392 g
25 Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).	

The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layering.

Example 15

5

Preparation of enteric coating layered pellets with silicon dioxide seeds.

Core material

	Magnesium omeprazole	8.00 kg
10	Silicon dioxide	8.00 kg
	Hydroxypropyl methylcellulose	1.41 kg
	Sodium lauryl sulphate	0.08 kg
	Water purified	28.00 kg

15 Separating layer

Core material (acc. to above)	10.00 kg
Hydroxypropyl methylcellulose	0.80 kg
Water purified	10.00 kg

20 Enteric coating layer

Pellets covered with separating layer (acc. to above)	300 g
Methacrylic acid copolymer	124 g
Polyethylene glycol 400	25 g
Mono- and diglycerides (NF)	3 g
25 Polysorbate 80	1 g
Water purified	463 g

30 Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved binder and a surface active ingredient.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

Example 16

Preparation of enteric coating layered pellets.

10

Enteric coating layer

Pellets covered with separating layer

(manufacturing and composition

as in example 13)

500 g

15

Methacrylic acid copolymer

250 g

Polyethylene glycol 6000

75 g

Mono- and diglycerides (NF)

12.5 g

Polysorbate 80

1.2 g

Water purified

490 g

20

Example 17

Preparation of enteric coating layered pellets.

25

Enteric coating

Pellets covered with separating layer

500 g

(manufacturing and composition as in example 1)

Hydroxypropyl methylcellulose phthalate

250 g

Cetanol

50 g

30 Ethanol (95%)

1000 g

Acetone	2500 g
---------	--------

Example 18

5 Preparation of enteric coating layered pellets.

Core material

Omeprazole	225 g
Mannitol	1425 g
10 Hydroxypropyl cellulose	60 g
Microcrystalline cellulose	40 g
Lactose anhydrous	80 g
Sodium lauryl sulphate	5 g
Disodium hydrogen phosphate dihydrate	8 g
15 Water purified	350 g

Separating layer

Core material (acc. to above)	300 g
Hydroxypropyl cellulose	30 g
20 Talc	51 g
Magnesium stearate	4 g

Enteric coating layer

Pellets covered with separating layer (acc. to above)	300 g
25 Methacrylic acid copolymer	140 g
Triethyl citrate	42 g
Mono- and diglycerides (NF)	7 g
Polysorbate 80	0.7 g

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed 5 apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm. The prepared core material is covered with a separating layer and enteric coating layered as described in previous examples.

Preparation of active substance.

10

Magnesium omeprazole used in the examples is produced according to the process described in WO/SE94/00680, omeprazole is produced according to the process disclosed in EP-A1 0005129, and the single enantiomers of omeprazole salts are produced as described in WO/SE94/00509. These documents are hereby incorporated in a whole by 15 reference.

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with at least one antibacterial compound and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components.
2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.
3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.
4. A dosage form according to claim 1, wherein the dosage form comprises an acid susceptible proton pump inhibitor and two antibacterial compounds.
5. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole or its single enantiomers or an alkaline salt thereof.
6. A dosage form according to claim 1, wherein the proton pump inhibitor is (s)-omeprazole magnesium salt.
7. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole.
8. A dosage form according to any of claims 5 - 7, wherein the antibacterial compound is clarithromycin and/or metronidazole.
9. A dosage form according to any of claims 5 - 7, wherein the antibacterial compound is amoxicillin and/or clarithromycin or metronidazole.

10. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-80 mg and the amount of antibacterial compound(s) is in the range of 100-900 mg.

5 11. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 20-40 mg and the amount of antibacterial compound(s) is in the range of 250-650 mg.

10 12. A tableted dosage form according to claim 2, wherein the dosage form consists of two separate layers, each one comprising different active substance(s).

13. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the acid susceptible proton pump inhibitor in the form of individually enteric coating layered pellets compressed together with an 15 antibacterial granulation into a tablet, whereby the enteric coating layer covering the individual pellets has mechanical properties such that the tableting of the pellets together with the antibacterial granulation and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the individually enteric coating layered pellets.

20 14. A tableted dosage form according to claim 13, wherein the acid resistance of the individually enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

25 15. A tableted dosage form according to 13, wherein the acid resistance of the individually enteric coating layered pellets does not decrease more than 10 % during the compression of the individual pellets into the multiple unit tableted dosage form.

30 16. A tableted dosage form according to claim 13, wherein the enteric coating of the individual pellets comprises a plasticized enteric coating layer material.

17. A tableted dosage form according to claim 13, wherein the individually enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.

5

18. A tableted dosage form according to claim 13, wherein the enteric coating layered pellets consist of a seed layered with the proton pump inhibitor.

10

19. A tableted dosage form according to claim 13, wherein the tablet is divisible.

15

20. A tableted dosage form according to claim 19, wherein the tablet is dispersible to a suspension of individually enteric coating layered pellets in an aqueous liquid.

20

21. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating layered tablet, optionally with a separating layer under the enteric coating layer and the tablet comprises at least two different pharmaceutically active substances in admixture with each other.

25

22. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor and one or more antibacterial compounds in a capsule, characterized in that the proton pump inhibitor is prepared in the form of individually enteric coating layered pellets and the pellets are filled into a capsule together with the antibacterial compound(s) optionally mixed with pharmaceutically acceptable excipients.

30

23. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor and one or more antibacterial compounds in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of individually enteric coating layered pellets and these pellets are mixed with a prepared antibacterial granulation and optionally pharmaceutically acceptable tablets excipients whereafter the dry mixture is compressed into a multiple unit tablet without

giving any significant change of the acid resistance of the enteric coating layer covering the individually enteric coating layered pellets.

24. A process for the manufacture of a fixed dosage form comprising an acid
5 susceptible proton pump inhibitor and one or more antibacterial compound(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with the antibacterial compound(s) and pharmaceutically acceptable excipients whereafter the dry mixture is compressed into a tablet, which tablet is covered with an enteric coating layer and optionally a separating layer is applied onto the tablet before the enteric coating layer.

10

25. A dosage form according to any of claims 1 to 21 for use in the treatment of disorders associated with *Helicobacter* infections in mammals and man.

26. A dosage form according to claim 25, wherein the disorder is a gastric disorder
15 associated with *Helicobacter pylori* infections.

27. A method for the treatment of disorders associated with *Helicobacter* infections in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 21.

20

28. A method according to claim 27, wherein the disorder is a gastric disorder associated with *Helicobacter pylori* infections.

29. Use of a dosage form according to any of claims 1 to 21 for the manufacture of a
25 medicament for the treatment of disorders associated with *Helicobacter* infections in mammals and man.

30. Use of a dosage form according to claim 29, wherein the disorder is a gastric disorder associated with *Helicobacter pylori* infections.

1 / 1

Fig. 1

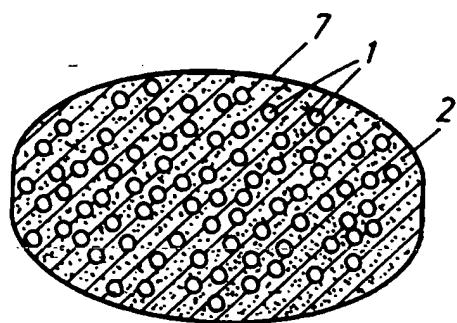


Fig. 2

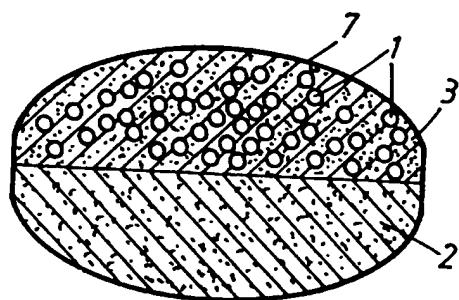


Fig. 3

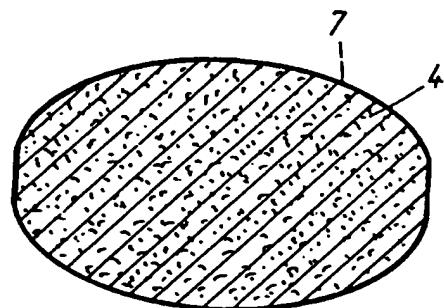
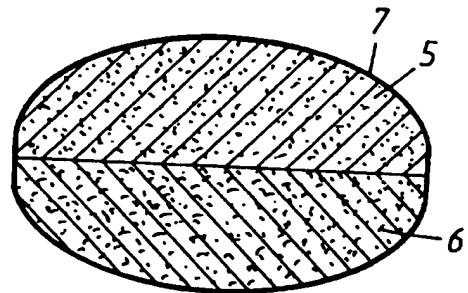


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/44, A61K 31/71, A61K 31/41, A61K 31/43, A61K 9/20, A61K 9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, USFULLTEXT, CLAIMS, EMBASE, MEDLINE, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	EP 0642797 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 15 March 1995 (15.03.95) --	1-26
Y	WO 9211849 A1 (THE PROCTER & GAMBLE COMPANY), 23 July 1992 (23.07.92), page 3, line 24 - line 32; page 7, line 22 - line 24 --	1-26
Y	Dialog Information Services, File 73, EMBASE, Dialog accession no. 9150953, EMBASE accession no. 94095444, Logan R.P.H. et al: "Eradication of Helicobacter pylori with clarithromycin and omeprazole", GUT (United Kingdom), 1994, 35/3 (323-326) --	1-26

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" prior document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

9 May 1996

Date of mailing of the international search report

10-05-1996

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Anneli Jönsson
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90) -- -----	1-26

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 27-30
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00125

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A1- 0642797	15/03/95	NONE		
WO-A1- 9211849	23/07/92	AU-A- US-A-	1252592 5128140	17/08/92 07/07/92
EP-A1- 0365947	02/05/90	SE-T3- AU-B,B- AU-A- CA-A- DE-T- ES-T- HK-A- IE-B- JP-A- LV-B- PT-B- SE-A- SG-A- US-A-	0365947 612525 4365089 2000932 68907177 2055775 123394 62640 2164821 10382 92103 8803822 123894 5178868	11/07/91 03/05/90 26/04/90 13/01/94 01/09/94 18/11/94 22/02/95 25/06/90 20/12/95 09/08/95 26/10/88 17/03/95 12/01/93